Emerging Concepts in the Neurobiology of Chronic Pain: Evidence of Abnormal Sensory Processing in Fibromyalgia

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Chronic pain often differs from acute pain. The correlation between tissue pathology and the perceived severity of the chronic pain experience is poor or even absent. Furthermore, the sharp spatial localization of acute pain is not a feature of chronic pain; chronic pain is more diffuse and often spreads to areas beyond the original site. Of importance, chronic pain seldom responds to the therapeutic measures that are successful in treating acute pain. Physicians who are unaware of these differences may label the patient with chronic pain as being neurotic or even a malingerer. During the past decade, an exponential growth has occurred in the scientific underpinnings of chronic pain states. In particular, the concept of nonnociceptive pain has been refined at a physiologic, structural, and molecular level. This review focuses on this new body of knowledge, with particular reference to the chronic pain state termed “fibromyalgia.”

LESSONS OF EPIDEMIOLOGY

Nonmalignant chronic musculoskeletal pain is commonly encountered in the general population. Patients with this symptom often have areas of hyperalgesia in muscles and nearby structures—so-called tender points. In a postal survey of 2,034 adults in northern England, Croft and associates reported prevalence rates of 11.2% for chronic widespread pain, 43% for regional pain, and 44% for no pain. When subjects with widespread pain were examined, 21.5% had 11 or more tender points, 63.8% had between 1 and 10 tender points, and 14.7% had no tender points. In general, a positive correlation was noted between the finding of a tender point and a history of pain in that site. Furthermore, the number of tender points did not necessarily correlate with widespread pain but did correlate with depression, fatigue, and poor sleep—independent of pain status. Wolfe and colleagues conducted a similar study in Wichita, Kansas, and they found that the prevalence of chronic widespread musculoskeletal pain was more common in women than in men and that it increased progressively from ages 18 to 70 years—prevalence was 23% in the seventh decade of life. Chronic regional pain had a similar prevalence in men and women and displayed an almost linear increase with age, approximately 30% by the eighth decade of life (Fig. 1). Other studies, however, have described chronic pain peaking during middle age. Gagliese and Melzack recently reviewed the possible reasons for this discrepancy. The American College of Rheumatology defined the condition of fibromyalgia as
accompanied by symptoms of fatigue, nonrestorative sleep, and a potpourri of somatic symptoms that lack a well-defined causation. A subset of patients with severe, intractable pain experience pain on light touch; this is referred to as allodynia. Thus, the spectrum of chronic pain ranges from transient local pain to intractable widespread pain with allodynia (Fig. 2). For most physicians, the confusing feature of chronic pain is the lack of a relationship between the extent of nociceptive stimulus and the intensity of the pain. The experimental basis for understanding this paradox is the focus of the rest of this article.

**PATHOPHYSIOLOGIC BASIS FOR CHRONIC NONMALIGNANT PAIN**

The International Association for the Study of Pain defines pain as follows: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” This definition explicitly affirms that pain has both a sensory and an affective-evaluative component and acknowledges that pain may occur in the absence of obvious peripheral or visceral pathologic features. To comprehend chronic pain, one must integrate the sensory and affective-evaluative elements of the pain experience. Focusing exclusively on the psychologic aspects of pain or addressing only the sensory component and ignoring the affective dimensions are equally misguided approaches. For clarity, each of these two constitutive elements will be discussed separately.

**Sensory Component**

Pain is generally viewed as the perceptual result of a cascade of impulses that originates from nociceptors in somatic or visceral tissues. The impulses travel in peripheral nerves, with a first synapse in the dorsal horn and a second synapse in the thalamus, and end up in the cerebral cortex and other supraspinal structures. This results in a pain experience and the activation of reflex and reflective behaviors. These reflex and reflective behaviors are aimed at eliminating further pain. The expectation is that nociceptor-driven pain will be successfully abolished, an outcome that facilitates healing and resumption of a pain-free state. With chronic pain, however, the linear relationship between nociception and pain experience is inappropriate or even absent, and the expected recovery does not occur. Compelling evidence shows that patients with fibromyalgia have these qualitative differences in their pain perception.

An objective measure of applied force to a tender point can be obtained by dolorimetry. Various instruments have been used, the most common of which is a spring-loaded balance or an electric palpometer. In a recent study, an
electric palpometer was used to record the subject’s assessment of pain intensity on a 0- to 10-cm visual analogue scale, at varying levels of applied force. Distinctly different response curves were obtained between control subjects and patients with fibromyalgia. In pain-free control subjects, the threshold of pain was at approximately 160 dolorimeter unit; beyond that, the increase in pain intensity was almost linear. In contrast, patients with fibromyalgia exhibited a linear increase in pain from the baseline dolorimeter force of 80 units. The calculated areas under the two curves were 3,952 and 2,165 for those with fibromyalgia and control subjects, respectively (P = 0.002). This demonstration of qualitatively altered nociception in patients with fibromyalgia suggests that these patients differ from pain-free subjects in their processing of sensory information. Theoretically, this difference could result from (1) sensitization of peripheral nociceptors (but this would be expected to produce quantitative change in the response curve), (2) a decrease in the activity of the descending inhibitory pathway (but this would be expected to produce a parallel shift to the left), or (3) changes in the central processing of pain at the spinal level (the most likely explanation). Similar abnormalities of processing pain in patients with fibromyalgia have also been reported for heat, cold, and auditory stimuli. When a muscle is isometrically contracted, normally the pain threshold increases on palpation. In patients with fibromyalgia, the pain threshold decreases. Investigators have hypothesized that this is a result of either sensitization of mechanoceptors in fibromyalgia or dysfunction of afferent inhibition activated by muscle contraction, as per the gate control theory of pain. Whatever the mechanism, it partially explains the increased pain on exertion that is experienced by patients with fibromyalgia.

A common misconception is to view the nervous system as being “hard wired”—that is, stimulation of a nerve ending (for example, a needle prick) always produces the same behavioral and affective response. This concept implies that the same intensity of noxious stimulus will always elicit the same degree of nerve stimulation and hence the same subjective experience of pain. Investigators now know that this concept is wrong. More than 30 years ago, Melzack and Wall proposed that pain is a complex integration of noxious stimuli, affective traits, and cognitive factors. The emotional aspect of a chronic pain state and the rationalization of the problem may influence the final experience of pain. In 1965, Mendell and Wall provided the first experimental evidence that the nervous system is not hard wired. They noted that repetitious stimulation of a peripheral nerve, at sufficient intensity to activate C fibers, resulted in a progressive buildup of the magnitude of the electrical response recorded in the second order dorsal horn neurons. If the system were hard wired, each stimulus would have elicited the same response in the second order neuron. They termed this phenomenon “wind-up.” Investigators now appreciate that the phenomenon of wind-up is crucial to understanding chronic pain. Furthermore, the biochemical basis for this phenomenon is now being unraveled. An example of an experiment demonstrating wind-up is shown in Figure 3. This experiment also demonstrates an important property of wind-up—it is dependent on activation of N-methyl-D-aspartate (NMDA) receptors. Prior treatment of an animal with AP5, an NMDA receptor antagonist, prevented the summation of the signal at the level of the spinal cord. The wind-up phenomenon provides an explanation for the manner in which persistent stimulation of peripheral nerves can lead to a disproportionate up-regulation of the central nervous system. This augmented sensory processing has been referred to as nonnociceptive pain (NNP). NNP may be defined as the experience of pain elicited by the stimulation of nerve fibers that normally relay nonpainful sensations to the spinal cord (that is, nonnociceptive neurons). This occurs because the nonnociceptive afferents are acting on a sensitized central nervous system, not because they are dysfunctional.

The four characteristic clinical features of NNP (Table 1) are as follows: (1) the description of pain seems inappropriate in comparison with the degree of tissue pathology, or no tissue pathology may be discernible; (2) noxious stimuli result in a pain experience that is greater and more unpleasant than would normally be expected (that is,
Sensory input from muscle, as opposed to skin, is a substantially more potent effector of central sensitization. This may be the clue to the role of muscle pain in the total spectrum of the fibromyalgia syndrome. In 1984, Wall and Woolf used a decerebrate rat model to explore the effects on reflex withdrawal of the hind limb to a noxious stimulus (pinching the paw). The pain stimulus was applied both before and after stimulation of either the sural nerve (a purely cutaneous nerve) or the gastrocnemius-soleus nerve (a predominantly muscle afferent) at 1 Hz for 20 seconds. Stimulation of the sural nerve induced an increased excitability of the withdrawal reflex that lasted about 10 minutes. Stimulation of the gastrocnemius-soleus nerve produced a prolonged increase in reflex activity that lasted up to 90 minutes. Of importance, these results were also seen in the contralateral limb, an indication of a central rather than a peripheral cause. These investigators surmised that intraspinal changes evoke the observed long-lasting reflex that occurs after stimulation of muscle afferent C fibers. More than a decade later, we now know that this experiment demonstrated the phenomenon of central sensitization. Furthermore, it showed that central sensitization is more strongly induced by afferent impulses from muscle nociceptors than from skin nociceptors.

Two studies of somatosensory-induced potentials directly support a state of central sensitization in patients with fibromyalgia. Somatosensory-induced potentials refer to the electrophysiologic activity that can be measured by skull electrodes in response to peripheral sensory stimulation. In their study of carbon-dioxide laser stimulation of skin, Gibson and associates reported an increased late nociceptive-evoked somatosensory response in 10 patients with fibromyalgia in comparison with 10 matched control subjects. Moreover, Lorenz and colleagues recently described increased amplitude of the N170 and P390 brain somatosensory potentials in patients with fibromyalgia in comparison with control subjects after laser stimulation of the skin (Fig. 4). Furthermore, they observed a response in both hemispheres in the patients with fibromyalgia; in control subjects, the somatosensory potential was strictly localized to one side of the brain. These investigators controlled for increased hypervigilance (a psychologic concept related to a conditioned expectation response) by using interspersed auditory stimuli; the somatosensory potentials to these stimuli in the patients with fibromyalgia were the same as those in the control subjects. These two studies provide objective evidence that patients with fibromyalgia have an augmented central processing of nociceptive stimuli in comparison with pain-free control subjects.

The two types of second order spinal neurons involved in central sensitization are nociceptive-specific neurons, which respond only to nociceptive stimuli, and wide dy-

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**Table 1. Sensory Findings in Patients With Nonnociceptive Pain**

<table>
<thead>
<tr>
<th>Tissue pathology</th>
<th>Poor correlation with tissue pathology or no pathology</th>
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<tr>
<td>Quantitative</td>
<td>Hyperesthesia, hyperalgesia</td>
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<tr>
<td>Qualitative</td>
<td>Allodynia, dysesthesia, paresthesia</td>
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<tr>
<td>Spatial</td>
<td>Radiation, centrifugal spread</td>
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<td>Temporal</td>
<td>Increased latency, after sensation, abnormal summation</td>
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dynamic range neurons, which respond to both nociceptive and nonnociceptive afferent stimuli. Both may be sensitized by noxious stimuli, but wide dynamic range neurons are generally more intensely sensitized than are nociceptive-specific neurons. Nociceptive and nonnociceptive afferents often converge onto the same wide dynamic range neuron (Fig. 5). After sensitization by ongoing nociceptive impulses from peripheral nerves, wide dynamic range neurons will respond to nonnoxious stimuli as intensely as they had to noxious stimuli before sensitization. This results in sensations such as light touch being experienced as pain (that is, allodynia). A common example of such central sensitization is postherpetic neuralgia. Previous injury to a peripheral nerve leads to an amplification of both nociceptive and nonnociceptive impulses. The mechanism responsible for the abnormal perception of nonnociceptive impulses in postherpetic neuralgia is the activation of wide dynamic range neurons in the dorsal horn of the spinal cord. A pressure block can experimentally validate the involvement of nonnociceptive afferent axons in neuropathic pain. Nerve compression (with use of a tourniquet) blocks transmission in nonnociceptive axons (that is, myelinated type A fibers) but not nociceptive unmyelinated type C fibers. Such a pressure block relieves allodynia but not normally noxious stimuli (a confirmation that the nociceptive afferents are still functional).25

Arroyo and Cohen26 described a similar conversion of nonnociceptive stimuli to unpleasant sensations while attempting to treat patients with fibromyalgia by using electrical nerve stimulation that would elicit only nonpainful sensations in normal persons. They noted that the pain was exacerbated and often caused dysesthetic sensations. In comparison with control subjects, patients with fibromyalgia had a reduced pain tolerance and two unexpected phenomena: a spread of dysesthesia (mainly tingling and burning) that was felt both distally and proximally to the stimulator and a persistence of dysesthesia around the stimulated locus that lasted for 12 to 20 minutes after the stimulation was terminated. Thus, electrical stimulation of the skin in patients with fibromyalgia results in phenomena that are characteristic of secondary hyperalgesia. Primary hyperalgesia is the normal perception of pain from nociceptor stimulation of injured tissue. Secondary hyperalgesia refers to pain elicited from uninjured tissues. Torebjörk and associates28 convincingly demonstrated this phenomenon in humans. Thus, Arroyo and Cohen’s inadvertent experiment provides evidence for altered nonnociceptive processing in patients with fibromyalgia.

Sensitization of wide dynamic range neurons by prior noxious stimuli provides the pathophysiologic foundation for NNP. Evidence is emerging that afferent activity from

Fig. 4. Laser-induced skin pain results in significantly increased electroencephalographic potentials at 170- and 390-ms peaks in patients with fibromyalgia (FM) in comparison with control subjects (Cntrl). (Modified from Lorenz and associates.27 By permission.)

Golgi tendon organs and muscle spindles may activate pain-related central neurons if those neurons have been sensitized. For instance, some patients with stroke and spinal cord injuries have development of severe pain on movement. Berić31 proposed the term “proprioceptive allodynia” to describe this phenomenon. He describes such patients as follows: “While these patients may not experience any spontaneous pain at rest, they develop excruciating burning and tingling, sometimes impossible to describe in words, which appears only when they try to hold an object, move a limb, stand or walk.” Thus, everyday muscle activity may cause pain and impair function in some patients with central sensitization. At a physiologic level, pain on movement (in the absence of tissue damage or a metabolic disorder) implies that proprioceptive afferents are activating second order wide dynamic range spinal neurons that have been sensitized by previous nociceptive activity.

The central nervous system of people who have ongoing pain (for example, reflex sympathetic dystrophy) or who have had previous pain experiences (for example, after an injury) may be permanently altered due to changes that are now understood at the physiologic, molecular, and structural levels. Clinically, persistent pain in survivors of serious illnesses who experienced high levels of pain during hospitalization33 or persistent pain after breast surgery34 may reflect ongoing central sensitization that remains even after healing of peripheral tissue injury. Likewise, fibromyalgia seldom develops unexpectedly. Although some patients attribute stress, infections, and toxins to onset of fibromyalgia, most relate an injury, repetitive work-related...
pain, athletic injuries, or another pain state. For instance, fibromyalgia is commonly found as an accompaniment to rheumatoid arthritis,\textsuperscript{35,36} low-back pain,\textsuperscript{37,38} systemic lupus erythematosus (SLE),\textsuperscript{39,40} and osteoarthritis. A recent study from Israel documented a 22\% prevalence of fibromyalgia 1 year after automobile accidents causing whiplash in comparison with a 1\% prevalence after accidents involving leg fractures.\textsuperscript{41} These findings suggest that nociceptive afferent input from neck muscles is a potent inducer of central sensitization. Most injured persons, however, do not have development of fibromyalgia, and only 20 to 35\% of patients with rheumatoid arthritis or SLE have a concomitant fibromyalgia syndrome. Thus, persons who are destined to have development of fibromyalgia are either genetically predisposed (nature) or have past life events or experiences that favor its later development (nurture). Interestingly, patients with fibromyalgia have an increased prevalence of other pain-dysesthetic disorders such as irritable bowel syndrome, female urethral syndrome, and restless legs syndrome.\textsuperscript{42-44} Possibly, abnormal processing of normally nonnociceptive afferent impulses facilitates the expression of these commonly associated syndromes. Speculating whether the afferent input from these associated conditions has a role in the maintenance of central sensitization is also germane. This could occur through the extensive convergence of visceral and muscle afferents onto second order wide dynamic neurons in the dorsal horn. Chronic pain states may also develop during or after some infections\textsuperscript{45-49} or in association with ongoing inflammatory diseases such as SLE.\textsuperscript{50} The scientific basis for this common observation is now being elucidated in a complex neural pathway involving proinflammatory cytokines (interleukin-1 and 6 and tumor necrosis factor) that activate vagal afferents. Subsequent stimulation of the nucleus magnus raphae activates descending spinal tracts, which sensitize second order dorsal horn neurons through an NMDA-substance P-nitric oxide cascade\textsuperscript{51-56} (Fig. 6).

The reason that the phenomenon of long-lasting central sensitization occurs only in a minority of persons is currently unknown. One possibility that has gained some support is a genetic susceptibility based on the striking familial occurrence in female relatives of patients with fibromyalgia.\textsuperscript{57,58} At a molecular level, many studies have demonstrated the important role of excitatory amino acids, such as glutamate, and neuropeptides, such as substance P, in the generation of central sensitization.\textsuperscript{59-63} Substance P is an important nociceptive neurotransmitter. It lowers the threshold of synaptic excitability, an outcome allowing the unmasking of normally silent interspinal synapses and the sensitization of second order spinal neurons.\textsuperscript{64-66} Activation of NMDA receptors has a permissive effect on release of substance P into the dorsal horn.\textsuperscript{67} Furthermore, substance P can extend long distances in the spinal cord and sensitize dorsal horn neurons at some distance from the
initial input locus. This results in an expansion of receptive fields and the activation of wide dynamic neurons by nonnociceptive afferent impulses. These alterations in the dorsal horn can be experimentally documented as an increased internalization of substance P receptors, an increased expression of c-fos (a proto-oncogene induced by increased neuronal activity), and persistent structural changes. A recent study showed that activation of NMDA receptors in the spinal cord causes a release of substance P and dramatic structural changes in the dendrites of neurons having substance P receptors. Clinically, these phenomena would seem to be an expansion of receptive fields—for example, the perception of pain in apparently uninjured sites after an automobile accident. An increased production of neurotransmitters within the spinal cord may be detected as increased levels in cerebrospinal fluid. Two definitive studies have shown a threefold increase of substance P in the cerebrospinal fluid of patients with fibromyalgia in comparison with control subjects. An animal model of hyperalgesia that indicates substance P as a major etiologic factor in central sensitization has highlighted the probable relevance of substance P in human pain states. Thus, the finding of increased levels of substance P in patients with fibromyalgia is in accord with the theory that central sensitization is relevant to the pathogenesis of fibromyalgia. The perception of pain is down-regulated by an endogenous antinociceptive system that is activated by noxious stimuli and stress. The neurons involved in this antinociceptive activity originate in the periaqueductal gray matter and rostral ventromedial medulla. The neurotransmitters involved seem to be γ-aminobutyric acid and met-enkephalin, respectively. Second order neurons are also modulated through afferent activity in descending antinociceptive spinal tracts. Inhibition of this modulatory system may also eventuate in activation of otherwise silent intraspinal synapses, with a resultant expansion of receptive fields. Thus, a defect in the spinal descending inhibitory pathways would lead to both an amplification of muscle afferent impulses and a spread to adjacent myotomes. At the spinal
level, the major neurotransmitter in this descending system is serotonin.76

Down-regulation of pain threshold can be demonstrated in normal persons by subjecting them to repeated skin stimulation. This strategy is the basis for the use of transcutaneous nerve stimulators in the management of chronic pain states. The physiologic basis for this effect is the inhibition of all dorsal horn neurons (including wide dynamic neurons) to persistent stimulation of type A myelinated axons, as originally described by Wall and Cronly-Dillon in 1960.77 This effect, known as diffuse noxious inhibitory control, was investigated in 25 female patients with fibromyalgia and 26 age-matched healthy women.78 Tonic thermal stimuli at painful and nonpainful intensities were used to induce pain inhibition. The patients with fibromyalgia had significantly lower heat pain thresholds than did the healthy subjects but similar electrical detection and pain thresholds. Concurrent tonic thermal stimuli, at both painful and nonpainful levels, significantly increased the electrical pain threshold in the healthy subjects but not in the patients with fibromyalgia. The investigators concluded that diffuse noxious inhibitory control was deficient in patients with fibromyalgia, a suggestion that these patients had deficient pain modulation or were unable to tolerate a tonic stimulus of sufficient intensity to stimulate a down-regulatory response.

Psychologic Component

As previously stated, chronic pain can occur in the absence of ongoing tissue damage; this is an example of the sensory component of pain. Moreover, one component of pain is an avoidance behavior that can occur before the conscious appreciation of pain. In terms of brain physiology, this implies that primitive parts of the brain are being activated (that is, the areas below the cerebral cortex). These subcortical areas of the brain contain several discrete nuclei (for example, the thalamus, cingulate gyrus, hippocampus, amygdala, and locus ceruleus) that interact to form a functional unit called the limbic system. This part of the brain subserves many affective phenomena, including the association of sensory input with specific mood states (for example, pleasure, fear, and aversion). These facts form the physiologic basis for considering the emotional aspect of pain. Interestingly, electrical stimulation of the brain during neurosurgical procedures does not induce pain sensations in pain-free subjects. In patients with a past history of pain, however, it often reawakens previous pain experiences.79 Investigators surmise that such stimulation reacti- vates cortical and subcortical pain circuits that were previously dormant. A known fact is that no single cortical structure subserves pain memory. Recent studies of amputees with phantom limb have shown that stimulation of the ventrocaudal thalamus can evoke phantom pain.80 Thus, a “reawakening” of neural circuits in the thalamus could be a mechanism whereby purely psychologic mechanisms trigger pain memories. The current theory is that different cortical and subcortical structures seem to be involved in different aspects of the pain experience. For instance, removal of the somatosensory cortex does not abolish chronic pain, but excision of lesions in the anterior cingulate cortex reduces the unpleasantness of pain.81,82 The anterior cingulate cortex is involved in the integration of affect, cognition, and motor response aspects of pain83,84 and exhibits increased activity on positron emission tomography and functional magnetic resonance imaging of patients with pain.85-87 Other structures involved in cortical pain processing include the prefrontal cortex (activation of avoidance strategies, diversion of attention, and motor inhibition), the insula (alerting mechanisms and integration of other relevant sensations), the amygdala (emotional state and activation of hypervigilance), and the locus ceruleus (activation of the “fight or flight” response).88 All these structures are linked to the medial thalamus, whereas the lateral thalamus is linked to the somatosensory cortex (pain localization). Lesions of the lateral thalamus (for example, strokes) often result in a contralateral pain syndrome characterized by aching, burning, and tingling pain that is exacerbated by normally innocuous stimuli such as light touch (that is, alldynia); affective distress is often a prominent clinical feature.89 This is considered a consequence of disinhibition of the medial thalamus with resultant activation of a limbic network that involves the anterior cingulate.90,91 Modern imaging techniques have demonstrated a relationship between reduced thalamic blood flow and some chronic pain states.92-95 The reduced thalamic perfusion described in chronic pain is in contradistinction to acute pain, in which increased perfusion has been noted.96-98 With use of single-photon emission computed tomography, Mountz and colleagues95 showed that patients with fibromyalgia, characterized by low pain thresholds, had a decreased regional blood flow in comparison with healthy control subjects. The decreased perfusion was particularly prominent in the thalamic and caudate nuclei (structures involved in the processing of nociceptive stimuli). A similar finding was reported in patients with unilateral chronic neuropathic pain in which the oxygen-15 positron emission tomographic method was used.99 Thus, functional imaging studies are supportive of an altered processing of sensory input in patients with fibromyalgia.

The emotional component of pain is multifactorial and is shaped by past experiences, genetic factors, general state of health, psychologic distress, coping mechanisms, and beliefs and fears surrounding the pain diagnosis.100-105 Of importance, thoughts and other sensations can influence
the sensory pain input into consciousness as well as the emotional coloring of the pain sensation. Modulation of the flow of neural activity involved in pain by nonnociceptor activity and descending control pathways has been compared to a “gate.” Thus, thoughts (for example, beliefs, fears, depression, anxiety, anger, and helplessness) and peripherally generated sensations can dampen or amplify pain. Sleep disturbances are common in patients with chronic pain; a magnified perception of pain has been reported after a night of poor sleep. Moldofsky and coworkers described the common occurrence of disrupted sleep stages 3 and 4 by an α-δ rhythm in patients with fibromyalgia and the induction of a transient pain syndrome by disruption of sleep stages 3 and 4.

Varying degrees of functional disability commonly occur with chronic pain states. The reasons for dysfunction are multiple and vary from person to person. Pain often monopolizes attention (causes a lack of focus on the task at hand). It is usually associated with poor sleep (causes emotional fatigue) and often an augmented perception of pain. Movements may aggravate pain (causes a reluctance to engage in activity). Fear of activity often leads to deconditioning (which predisposes to muscle and tendon injuries and reduced stamina). Pain often causes stress, which may result in anxiety, depression, and inappropriate behavior (causes disability due to secondary psychologic distress).

The psychiatric diagnoses that are often considered in the differential diagnosis of chronic pain states are grouped under the heading of somatoform disorders. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders defines the somatoform disorders as follows:

...the presence of physical symptoms that suggest a general medical condition (hence, the term somatoform) and are not fully explained by a general medical condition, by the direct effects of a substance, or by another mental disorder (e.g., Panic Disorder). The symptoms must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

Somatization is defined as the communication of psychologic and interpersonal distress in terms of somatic symptoms that suggest an organic disease. Recent experiments have described an increase in the proto-oncogene c-fos in the brains of mice subjected to chronic stress. Of note, the augmented expression of c-fos is a standard technique for assessing neuroplasticity in experimental central pain states. Thus, this study provides potential insights into the central mechanisms whereby chronic psychosocial stress could lead to the occurrence of pain and abnormal behavior.

An ongoing debate is whether psychologic distress is due to chronic pain or whether it occurs as a complex interaction between pain and the patient’s intrinsic personality structure. Whether a general medical condition characterized by dysfunction of sensory processing (for example, fibromyalgia) should be classified as a somatoform disorder is definitely debatable. For instance, a psychiatric diagnosis that depends on the presence of physical symptoms that suggest a general medical condition and are not explained by a general medical condition will become a nonpsychiatric diagnosis once the general medical condition adequately explains the symptoms. Thus, the contemporary growth of knowledge regarding NNP will inevitably lead to a reappraisal of the concept of somatoform disorders.

RELEVANCE OF NNP

Physicians generally view pain as a symptom indicative of an underlying lesion (for example, abdominal pain in appendicitis). Failure to identify the cause of pain may have disastrous consequences for the patient; hence, the exhaustive investigation of this symptom can usually be justified to the patient and the insurers. When extensive investigations fail to detect an organic lesion as the cause for the pain, the symptoms may be considered “nonorganic,” a term often equated with functional or psychogenic disorders. Thus, physicians who are unaware of NNP may commit several errors: (1) order an array of expensive and sometimes risky (for example, exploratory surgery) investigations, (2) view the patient’s pain as being psychologic and use diagnostic labels such as somatization or malingering, (3) attempt to treat NNP as if it were nociceptive (for example, surgery), or (4) fail to recognize that some conditions have both nociceptive pain and NNP (for example, rheumatoid arthritis) and treatments must be concurrently applied to both components.

MULTIPLE SYMPTOMS IN PATIENTS WITH FIBROMYALGIA

Patients with chronic pain, especially fibromyalgia, often have many symptoms other than pain, and these almost always include severe fatigue, poor sleep, and post-exertional pain. Other reported problems are abdominal pain, cold intolerance, sicca symptoms, unexplained bruising, fluid retention, chest pain, jaw pain, dyspnea, dizziness, tension-type headaches, paresthesia, depression, and anxiety. Some symptoms relate to specific syndromes whose prevalence seems to be increased, including irritable bowel syndrome, migraine, premenstrual syndrome, Raynaud’s phenomenon, female urethral syndrome, restless legs syndrome, and neurally mediated hypotension. The causes of these multiple symptoms are probably multifactorial. A complex interaction among disordered sensory processing, personality traits, and psychologic distress probably forms the basis for the generation of multiple somatic symptoms. Patients with fibro-
myalgia often display a hypervigilance, which may magnify somatic distress. They also have an increased prevalence of major depression and other manifestations of psychologic distress. Some investigators have defined fibromyalgia as a psychiatric diagnosis and use terms such as the “affective spectrum disorder.” Persons with fibromyalgia who do not seek medical attention (that is, nonpatients) have less psychologic distress in terms of anxiety and depression than those who receive active treatment. Interestingly, differences in psychologic distress between patients and nonpatients were eliminated after the investigators controlled for pain threshold and fatigue ratings. The conclusion was that psychiatric disorders are not intrinsically related to the generation of fibromyalgia symptoms, but a history of multiple lifetime psychiatric diagnoses may have a role in the decision to seek medical attention. The general consensus is that a chronic pain state is stressful, and the amount of stress, in part, depends on a person’s intrinsic coping mechanisms. Persistent stress often alters neuroendocrine rhythms, and this phenomenon has been explored in patients with fibromyalgia. These patients have been reported to have a paradoxic pattern of hypothalamic-pituitary axis perturbation, characterized by an exaggerated adrenocorticotrophic hormone (corticotropin) response to corticotropin-releasing hormone but a blunted adrenal secretion of cortisone. Bennett and coworkers described a growth hormone (GH) deficiency state in about one-third of patients with fibromyalgia. Interestingly, GH deficiency in adults has been associated with an array of symptoms similar to those described by patients with fibromyalgia: low energy, poor general health, reduced exercise capacity, muscle weakness, cold intolerance, impaired cognition, dyshymia, and decreased lean body mass. GH is also important in maintaining muscle homeostasis and one theory is that GH deficiency in patients with fibromyalgia may be a factor in the impaired resolution of muscle microtrauma. This theory received some support in a double-blind study showing that patients with fibromyalgia experienced an improvement when they received recombinant GH for 9 months. Thus, some of the multiple symptoms of fibromyalgia may be due to neuroendocrine dysfunction. Nevertheless, neuroendocrine abnormalities, which occur only in some patients, are most likely a secondary epiphenomenon probably part of a stress response to persistent symptoms, as has been described in other situations.

MANAGEMENT LESSONS FROM THE NEUROBIOLOGY OF CHRONIC PAIN

The central lesson is that chronic pain is not persistent acute pain and that chronic pain, including fibromyalgia, often has a nonnociceptive component related to the phenomenon of central sensitization. A large part of the problem in treating chronic pain is the common belief that patients are exaggerating and embellishing a trivial pain problem and if they were made of the “right stuff” they would improve. Questioning the veracity and moral fiber of the patient is not therapeutically helpful. The consequences of persistent chronic pain (as is the expected experience for most people) generate a varied mix of emotions and behaviors that are often counterproductive in coping with a chronic problem. Many of these changes would be appropriate for managing acute self-healing pain events but become a liability when dealing with chronic pain. The result of chronic pain is often depressive illness, marital discord, vocational difficulties, social withdrawal, sleep disorders, increasing fatigue, and inappropriate beliefs.

The hope is that early and effective management will minimize the secondary consequences of persistent pain. Currently, opiates are the most effective medications for managing most chronic pain states. Their use for fibromyalgia and other nonmalignant chronic pain conditions is often condemned because of ignorance regarding their propensity to cause addiction, physical dependence, and tolerance. Although physical dependence (defined as a withdrawal syndrome after abrupt discontinuation) is inevitable, this should not be equated with addiction. Addiction is a dysfunctional state occurring as a result of the unrestrained use of a drug for its mind-altering properties; manipulation of the medical system and the acquisition of narcotics from nonmedical sources are common. Addiction should not be confused with “pseudo-addiction,” a behavior generated by attempts to obtain appropriate pain relief in the face of undertreatment of pain. Opiates are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analogesics have failed. Tramadol (Ultram), which was introduced into the United States 3 years ago, is a centrally acting analgesic with an interesting dual mechanism of action (a weak µ-opioid agonist and an inhibitor of serotonin and norepinephrine reuptake); it is proving to be useful in the early management of chronic pain states, before scheduled opioids are used. Drug treatment of complex chronic pain should ideally be part of a structured program that includes education, treatment of depression and other psychologic issues, cognitive behavioral therapy, physical therapy, occupational therapy, and exercise. The hope is that the impressive advances that have been made in understanding pain at the physiologic, structural, and molecular levels will lead to novel therapies (for example, NMDA receptor antagonists and substance P antagonists) that will provide effective relief of both nociceptive pain and NNP. In this respect, two recent studies
from Sweden reported that intravenous administration of ketamine (an NMDA receptor antagonist) attenuates pain, increases pain threshold, and improves muscle endurance in patients with fibromyalgia.\(^{18,19}\) In some patients, a single intravenous infusion for 10 minutes (0.3 mg/kg) resulted in a significant decrease in pain, an outcome that persisted for up to 7 days. At this subanesthetic dose, ketamine was more potent than intravenous morphine (10 g) and intravenous lidocaine (5 mg/kg) therapy. This therapeutic demonstration helps to pinpoint altered pain processing at a molecular level in patients with fibromyalgia. Effective treatment of NNP should lead to a more enlightened understanding of the role of psychologic factors in maintaining chronic pain states. Furthermore, an important corollary to this new era of understanding is that the prevention of central sensitization, by adequate treatment of nociceptive pain, should be the foremost goal of acute pain management.\(^{180}\)

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